Available online at www.sciencedirect.com
SCIENCE DIRECT®
Mutation Research 592 (2005) 1–2
Fundamental and Molecular Mechanisms of Mutagenesis
www.elsevier.com/locate/molmut
Community address: www.elsevier.com/locate/mutres

Editorial

# Molecular epidemiology: Convergence between toxicology and epidemiology

Significant advances in our understanding of the causes of disease and the means for disease prevention are occurring at the interface between toxicology and epidemiology. By definition, toxicological science is based in the study of the adverse effects of chemicals on living organisms, including symptoms, mechanisms, treatments and detection of biological poisoning, especially the poisoning of people [1]. Epidemiology is the study of the distribution and determinants of disease (and health-related states) in specified populations, and the application of this study to control of health problems [2]. Toxicology and epidemiology have common interest in relating disease outcomes to dose, i.e. the amount of exposure to a substance, with toxicological science deriving primarily from the experimental model, and associated biologic measurements in the laboratory setting, while epidemiological science derives primarily from observational studies of free-living human populations.

## 1. Biomarkers—a common tool

Biomarkers are the link between toxicological and epidemiological sciences. Use of biomarkers to monitor exposure in the work environment was pioneered in the 1970s, first with respect to metals and organic solvents, then gradually expanding to a larger, more varied spectrum of exposures. The use of biomarkers expanded with the availability of a growing number of techniques for measuring effects at the cellular and molecular level. In molecular cancer epidemiology studies in particular, biomarkers derived from persistant molecular damage, such as DNA and protein adducts, gene mutations, loss of heterozygosity (LOH), gene promoter hypermethylation, and altered gene expression, often in combination with other types of biomarkers, are being assessed in tissues and body fluids for detection of increased risk, various etiologic factors, early detection, disease progression, and prognosis [3–8].

The aim of occupational and environmental epidemiology is to study the causal relations between exposure to exogenous agents and the development of disease. Use of these biomarkers improves our ability to understand causality by allowing more direct and more accurate measurement of exposure and outcome. Use of biomarkers may also enhance quantitative risk assessment, by providing more accurate data for establishing dose–response relationships and measuring exposure and by facilitating the extrapolation of results from experimental animals to human populations. Direct observation of a relationship between disease and exposure was considerably easier when exposure levels were high, as was the case in the 1960s and the beginning of the 1970s, whereas today, with changing environments and decreasing exposure levels, we need to evaluate subtler exposures and smaller risks.

## 2. Understanding disease mechanisms for improved prevention

In order to design a successful disease prevention program, we should ideally understand the natural history of the disease. Despite the progress made over the decades, the mechanisms by which exposures lead to disease are still often unknown. Use of molecular markers in toxicology and epidemiology holds promise for elucidating the mechanisms of disease development

0027-5107/$ – see front matter 
doi:10.1016/j.mrfmmm.2005.05.009

and progression. Gene–environment interactions play a central role in these biological processes. As many of the factors in gene–environment interactions are modifiable, they could provide a good starting point for primary prevention.

Similar to hereditary predisposition to a certain disease, individual susceptibility to a particular exposure can at least in part be mapped genetically. As a consequence of the rapid advances in methods for molecular genetics in the 1980s and 1990s, it appears inevitable that variations in the genome, i.e. genetic polymorphisms, contributing to individual susceptibility will be identified at an increasing pace [9]. Whether that will improve our ability to control occupational and environmental diseases is, however, unclear because the number of genes that contribute to susceptibility to many diseases is likely to be large, and the effects of individual variants or haplotypes may be weak. Thus, prevention needs to still focus on benefit from modifications to lifestyle and environmental factors, although information about biomarkers of susceptibility is likely to contribute to characterization of these high-risk populations.

## 3. Future steps

Large-scale characterization of human population genetic variation is well underway [10] and initial progress is being made in toxicogenomics, relating toxic exposures to gene and protein expression profiles [11]. Human genomic and proteomic tools are rapidly becoming an essential component of the molecular epidemiology armamentarium, allowing for a better evaluation of dose–disease relationships in population sub-groups at differential genetic susceptibility. Genetic characteristics and associated disease phenotypes may also impact on modulation of therapeutic outcomes [12].

The convergence point in molecular epidemiology of the toxicological and epidemiological sciences is providing new opportunities for understanding disease mechanisms and novel means for disease prevention. As all research in biomedical sciences, molecular epidemiology will need to progress towards a more comprehensive view of the underlying biological processes, applying global analyses to supplement endpoint-by-endpoint approaches.

Drs. Sy Garte and Stefano Bonassi, in the following, summarize work presented at the ICT-X Satellite Meeting on Molecular Epidemiology, Linking Toxicology to Epidemiology: Biomarkers and New Technologies, 8–10 July, 2004, in Haikko, Porvoo, Finland.

## References

[1] M.O. Amdur, J. Doull, C.D. Klaassen, Cassarett and Doull's Toxicology: The Basic Science of Poisons, McGraw-Hill, New York, 1993.
[2] Last 2001.
[3] S.A. Belinsky, Gene-promoter hypermethylation as a biomarker in lung cancer, Nat. Rev. Cancer 4 (2004) 707–717.
[4] S.S. Hecht, Tobacco carcinogens, their biomarkers and tobacco-induced cancer, Nat. Rev. Cancer 3 (2003) 733–744.
[5] M. Olivier, S.P. Hussain, C. Caron de Fromentel, P. Hainaut, C.C. Harris, TP53 mutation spectra and load: a tool for generating hypotheses on the etiology of cancer, IARC Sci. Publ. 157 (2004) 247–270.
[6] D.H. Phillips, Smoking-related DNA and protein adducts in human tissues, Carcinogenesis 23 (2002) 1979–2004.
[7] Y. Sekido, K.M. Fong, J.D. Minna, Molecular genetics of lung cancer, Annu. Rev. Med. 54 (2003) 73–87.
[8] D. Sidransky, Emerging molecular markers of cancer, Nat. Rev. Cancer 2 (2002) 210–219.
[9] S.P. Daiger, Was the human genome project worth the effort, Science 308 (2005) 362–364.
[10] R.A. Gibbs, J.W. Belmont, P. Hardenbol, et al., The International HapMap Project, Nature 426 (2003) 789–796.
[11] M.J. Khoury, R. Davis, M. Gwinn, M.L. Lindegren, P. Yoon, Do we need genomic research for the prevention of common diseases with environmental causes? Am. J. Epidemiol. 161 (2005) 799–805.
[12] M.R. Spitz, X.F. Wu, G. Mills, Integrative epidemiology: from risk assessment to outcome prediction, J. Clin. Oncol. 23 (2005) 267–275.

Richard B. Hayes *
*Division of Cancer Epidemiology and Genetics*
*National Cancer Institute, EPS 8114, Bethesda*
*MD 20892, USA*

Kirsti Husgafvel-Pursiainen
Harri Vainio
*Finnish Institute of Occupational Health*
*Topeliuksenkatu 41 aA, FIN-00250 Helsinki, Finland*

* Corresponding author. Tel.: +1 301 435 3973
fax: +1 301 402 1819
*E-mail address:* hayesr@exchange.nih.gov
(R.B. Hayes)

Available online 1 July 2005